FORM PTO-1390 (Modified) (REV 11-98) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: **101195-38**

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR): **09/743395**

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/DE99/02180	**12 July 1999 (12.07.99)**	**10 July 1998 (10.07.98)**

TITLE OF INVENTION

Method for Stabilization and Improvement of Gene Transfer into Mammalian Cells

APPLICANT(S) FOR DO/EO/US

Bernd Dorken; Gerhard Wolff; and Axel Schumacher

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☐ A copy of the International Search Report (PCT/ISA/210).
8. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
9. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
10. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
11. ☐ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 13 to 20 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☒ Certificate of Mailing by Express Mail
20. ☐ Other items or information:

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
09/743395	PCT/DE99/02180	101195-38

21. The following fees are submitted:.

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

		CALCULATIONS PTO USE ONLY
☐	Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2) paid to USPTO and International Search Report not prepared by the EPO or JPO	**$970.00**
☒	International preliminary examination fee (37 CFR 1.482) not paid to USPTO but Internation Search Report prepared by the EPO or JPO	**$840.00**
☐	International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO	**$690.00**
☐	International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4)	**$670.00**
☐	International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4)	**$96.00**

ENTER APPROPRIATE BASIC FEE AMOUNT =	**$840.00**	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☒ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).	**$130.00**	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	11 - 20 =	0	x $18.00	**$0.00**	
Independent claims	3 - 3 =	0	x $78.00	**$0.00**	
Multiple Dependent Claims **(check if applicable)**.			☐	**$0.00**	
TOTAL OF ABOVE CALCULATIONS =				**$970.00**	
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28) **(check if applicable)**.			☒	**$485.00**	
SUBTOTAL =				**$485.00**	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)).			+	**$0.00**	
TOTAL NATIONAL FEE =				**$485.00**	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).**			☐	**$0.00**	
TOTAL FEES ENCLOSED =				**$485.00**	
				Amount to be: refunded	$
				charged	$

☐ A check in the amount of to cover the above fees is enclosed.

☒ Please charge my Deposit Account No. **14-1263** in the amount of **$485.00** to cover the above fees.
A duplicate copy of this sheet is enclosed.

☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. **14-1263** A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

The correspondence address associated with Customer No. 27387

27387
PATENT TRADEMARK OFFICE

SIGNATURE

Bruce S. Londa
NAME

33,531
REGISTRATION NUMBER

January 9, 2001
DATE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
Atty's Docket No. 101195-38

APPLICANT : Bernd Dörken et al.

FILED : Concurrently Herewith

FOR : Method for Stabilization and Improvement of Gene Transfer into Mammalian Cells

PRELIMINARY AMENDMENT

Hon. Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Prior to examination, please amend the application as follows:

IN THE CLAIMS

Please amend the claims as set forth in the attached marked-up copy and clean copy. Claims 1-6 and 8-10 have been amended; use claim 7 has been cancelled and new claim 11 added.

REMARKS

The above amendments were made to place the application into proper United States Patent Format.

Respectfully Submitted,

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Claims

1.

A method ~~to~~ for stabilizeing and improveing the transfer of genetic material into mammalian cells ~~characterized by the fact that the~~, comprising the steps of expressing a chosen gene ~~of choice~~ or its cDNA ~~is expressed~~ in a given target cell ~~where at the same time~~and simultaneously expressing ~~the~~ cell cycle regulator p21 ~~is expressed~~.

2.

The ~~M~~method of claim 1 ~~characterized by the use of~~, wherein ~~known techniques to carry out the~~ gene transfer of naked DNA into ~~a~~ the given target cell is carried out by known techniques or by employing viral or non-viral vector systems.

3.

The ~~M~~method of claim 1 ~~or 2, characterized by~~ the gene ~~transfer~~ transfer is carried out using one or more chosen from the group consisting of retroviral, adenoviral, baculoviral, parvoviral vectors ~~and/or~~and herpes virus vectors.

4.

The ~~M~~method of claim 1 ~~to 3, characterized by, co-localization of~~ wherein the ~~trans~~gene of choice and the cDNA of p21 are co-localized on the same vector.

5.

The ~~M~~method of claim ~~1 to 3, characterized by localization of the transgene~~, wherein the gene of choice and the cDNA of p21 are localized on different vectors.

6.

The ~~M~~method of claim 1 ~~to 5~~, ~~where~~ comprising the steps of , in order, transferring ~~the~~a vector carrying the material for the expression of p21 ~~is transferred~~ into the target cell ~~first~~, followed by ~~the~~ vector coding for the ~~trans~~gene of choice, resulting in expression of p21 at ~~the~~ a time when the vector coding for the ~~trans~~gene of choice enters the cell.

~~7.~~

~~Use of overexpressed p21 to prevent apoptosis of target cells when a therapeutic gene is transferred~~

8.

A viral vector system ~~to~~ for ~~optimise~~ optimizing~~the~~ gene transfer ~~which is characterized by,~~ comprising a viral gene transfer vector that carries a cDNA coding for p21 ~~beside the~~ a transgene of choice or its cDNA ~~a cDNA coding for p21~~.

9.

A viral vector system ~~to~~ for ~~optimise~~ optimizing~~the~~ gene transfer ~~which is characterized by,~~ comprising

- a viral vector which codes for the transgene of choice or its cDNA and
- a second viral transfer vector carrying a cDNA that codes for p21

10.

~~A~~ The viral vector system of claim 8 ~~or 9 which is characterized by the fact that~~, wherein the viral vector system is chosen from the group consisting of one or more of an adenovirus-, retrovirus-, parvovirus-, herpes virus ~~and/or~~and baculovirus-vector.

11. (new) The viral vector system of claim 9, wherein the viral vector system is chosen from the group consisting of one or more of an adenovirus-, retrovirus-, parvovirus-, herpes virus and baculovirus-vector.

Claims

1.

A method for stabilizing and improving the transfer of genetic material into mammalian cells , comprising the steps of expressing a chosen gene or its cDNA in a given target cell and simultaneously expressing cell cycle regulator p21.

2.

The method of claim 1 , wherein gene transfer of naked DNA into the given target cell is carried out by known techniques or by employing viral or non-viral vector systems.

3.

The method of claim 1 the gene transfer is carried out using one or more chosen from the group consisting of retroviral, adenoviral, baculoviral, parvoviral vectors and herpes virus vectors.

4.

The method of claim 1 , wherein the gene of choice and the cDNA of p21 are co-localized on the same vector.

5.

The method of claim 1 , wherein the gene of choice and the cDNA of p21 are localized on different vectors.

6.

The method of claim 1 , comprising the steps of , in order, transferring a vector carrying the material for the expression of p21 into the target cell , followed by vector coding for the gene of choice, resulting in expression of p21 at a time when the vector coding for the gene of choice enters the cell.

8.

A viral vector system for optimizing gene transfer , comprising a viral gene transfer vector that carries a cDNA coding for p21beside a transgene of choice or its cDNA.

9.

A viral vector system for optimizing gene transfer , comprising

- a viral vector which codes for the transgene of choice or its cDNA and
- a second viral transfer vector carrying a cDNA that codes for p21

10.

The viral vector system of claim 8 , wherein the viral vector system is chosen from the group consisting of one or more of an adenovirus-, retrovirus-, parvovirus-, herpes virus and baculovirus-vector.

11. (new) The viral vector system of claim 9, wherein the viral vector system is chosen from the group consisting of one or more of an adenovirus-, retrovirus-, parvovirus-, herpes virus and baculovirus-vector.

Method for Stabilization and Improvement of Gene Transfer into Mammalian Cells

Description

The invention refers to a method for stabilization and improvement of gene transfer into mammalian cells which is characterized by overexpression of the gene of the cell cycle regulator $p21^{WAF1/CIP1}$ (p21) an inhibitor of cyclin-dependent kinases (CDK).

By the use of already known techniques, genes or their cDNA's are transported into target cells in order to express the corresponding protein product. To do so, there exist different methods like transfer of naked DNA or by the help of viral and/or non-viral transfer systems (vector). These transfer systems contain an expression cassette which carries the gene or its cDNA and, if necessary, a promoter into a target cell. Depending on the final goal, there is a great variety of methods to transfer a gene of choice into a given target cell. For the expression of the transgene the host cell is used to transform and translate the genetic information into the corresponding protein.

One limitation of the efficacy of such gene transfer techniques is the induction of programmed cell death (apoptosis) which, in turn, is dependent on different factors like type and dose of the vector and/or expression cassette construct used.

Immunological effects limit the efficacy of gene transfer in vivo like e.g. in adenovirus-mediated gene transfer. However, induction of apoptosis is one of the main mechanism that limits both, in vivo and in vitro efficacy.

Therefore, the underlying concept of the invention was to develop a method which can prevent the induction of apoptosis in a target cell during and/or after gene transfer and, consequently, improves the gene transfer into and/or prolongs the expression in a mammalian cell of choice.

The task is completed by the transfer of genetic material like a therapeutic gene which represents the DNA and/or cDNA of a gene that is defective and/or deleted in the disease to be treated and that the therapeutic gene is transferred by known gene transfer techniques, if necessary in conjunction with a promoter, and that after the transfer the therapeutic gene is expressed in the target cell. In agreement to the claims, a cDNA of the cell cycle regulator p21

will be expressed in parallel by gene transfer before, concomitant with or after the transfer or the therapeutic gene.

P21 is a known cell cycle regulator which prevents re-entry of senescent cells into cell cycle progression by blockage of cyclin-dependent kinases. This function includes different mechanisms like hypophosphorylation of the protein product of the Retinoblastoma Gene (Rb), binding to proliferating cell nuclear antigen (PCNA), binding to CDK-cyclin complexes like cyclin D-CDK4, cyclin E-CDK2, and cyclin A-CDK2. Whereas the interaction between p21 and PCNA prevents DNA replication, the interaction of p21 with cyclin dependent kinase complexes results in arrest of the cell cycle in the G_1-phase. The presence of p21 and of its cellular function is of vital importance for the survival of a cell. This importance is, for instance, illustrated by the fact, that there exist almost no mutations that are able to survive.

The invented method surprisingly prevents the induction of apoptosis of a target cell after gene transfer by overexpression of p21.

As known, eukaryotic cells replicate their genome only during a defined and limited period of time which is termed as phase of DNA synthesis (S-Phase) of the cell cycle. The cell cycle comprises four phases: G_1-phase, S-Phase, G_2-phase and Mitosis. The duration of each phase is rather constant. The G_1-phase lasts in fast proliferating cells between 2 and 20 hours, S-Phase between 6 and 10 hours, G_2-phase between 2 and 4 hours and Mitosis between 3 and 4 hours.

For gene transfer already known techniques are used, where the gene of choice can be transferred as naked DNA or by packaging it in different types of vectors which can be of non-viral or viral nature. Preferentially, viral vectors are used like adenovirus, retrovirus, baculovirus, parvovirus and/or herpes virus or others.

In correspondence to the invention, one application is performed by placing the cDNA of a given therapeutic gene and the cDNA of p21 in the same gene transfer vector.

Afterwards, the vector system is transferred into the target cell were the protein of choice and p21 are expressed.

Another preferred application is characterized by the fact that the cDNA of a given therapeutic gene and the cDNA of p21 are localized on different gene transfer vector. The transfection into the target cell takes place at the same time.

In another application, the vector which carries the material for the expression of p21 can be introduced into the target cell first. Afterward the vector which carries the transgene of choice

are transferred into the target cell, so that expression of p21 takes already place at the time when the vector with the therapeutic material is introduced.

Moreover, the invention encompasses also a viral vector system for the optimization of the gene transfer which is characterized by

- the nucleic acid of a viral vector containing the genetic material to be transferred and that of p21
- the nucleic acid of a viral vector containing the genetic material and the nucleic acid of a viral vector containing the genetic material of p21

Especially, adenovirus based gene transfer vectors are preferred. Therefore the invention will be explained in more detail using an example of adenovirus based gene transfer vectors.

One of the most commonly used vectors systems to transfer genetic material are adenovirus vectors (Ad vector). Because of their high titer and their stability in blood, the Ad vector is especially efficient for in vitro and in vivo gene transfer. Natural target cells for the adenovirus are epithelial based cells and tissue. After infection of replicating and/or non-replicating cells, the adenoviral genome is located in the nucleus in an epichromosomal fashion resulting in a temporary gene expression.

Fig. 1 demonstrates apoptosis of Ad vector infected cells exemplified by the use of an Ad vector which carries the gene for human alpha-1 antitrypsin. This takes place by activation of S-phase without subsequent mitosis leading to deformed polyploid nuclei.

In agreement with the claims, the Ad vector induced apoptosis of the target cells could be prevented by ectopic overexpression, i.e. co-expression, of the cell cycle regulator p21. Using the same type of Ad vector as in Fig. 1, the infected target cells survived and were free of deformed polyploid nuclei and no apoptosis occurred after adenovirus-mediated gene transfer of p21 (Fig. 2).

That p21 can indeed prevent Ad vector mediated apoptosis of the infected target cell can be seen in Fig. 3 which demonstrates that S phase activation can be prevented by adenovirus-mediated overexpression of p21.

Figure Legends

Figure 1

Replication-deficient recombinant adenovirus vector induces apoptosis by uncoupling of S-phase and mitosis. The corresponding flow cytometry analysis of cell cycle distribution (A, B) and in situ detection of apoptosis by TUNEL-assay (C, D) are demonstrated for LoVo cells 48 h after Ad vector infection. Cells were mock infected (buffer control) (A, C) or infected with an Ad vector carrying alpha-1 antitrypsin (100 plaque forming units per cell) (B, D).

Figure 2

Overexpression of p21 prevents adenovirus-induced apoptosis. In situ detection of apoptosis in LoVo cells 48 h after infection. Cells were mock infected with buffer (A, D), infected with an Ad vector carrying the human alpha-1 antitrypsin at a dose of 100 plaque forming units per cell (B, E) or infected with an Ad vector coding for p21 (100 plaque forming units per cell) (C, F). Shown are representative photographs at a magnification of 200-fold (A to C) and 600-fold (D to F).

Figure 3

P21 protects against adenovirus-mediated apoptosis by prevention of a G2-like arrest. Demonstrated is the flow cytometry analysis of cell cycle distribution of LoVo cells after 48 h of infection with different doses of Ad vectors expressing either the cDNA of human alpha-1 antitrypsin ( ) or the cDNA of p21 ( ). Shown are the relative percentages of the cell populations which are in the G_0/G_1 or G_2/M phase of the cell cycle as well as the percentage of living cells in the whole population (negative in the propidiumiodid staining; PI⁻). The data represent the mean ± standard error of three experiments.

Claims

1.

A method to stabilize and improve the transfer of genetic material into mammalian cells characterized by the fact that the gene of choice or its cDNA is expressed in a given target cell where at the same time the cell cycle regulator p21 is expressed.

2.

Method of claim 1 characterized by the use of known techniques to carry out the gene transfer of naked DNA into a given target cell or by employing viral or non-viral vector systems.

3.

Method of claim 1 or 2, characterized by gene transfer using retroviral, adenoviral, baculoviral, parvoviral vectors and/or herpes virus vectors.

4.

Method of claim 1 to 3, characterized by co-localization of the transgene of choice and the cDNA of p21 on the same vector.

5.

Method of claim 1 to 3, characterized by localization of the transgene of choice and the cDNA of p21 on different vectors.

6.

Method of claim 1 to 5, where the vector carrying the material for the expression of p21 is transferred into the target cell first followed by the vector coding for the transgene of choice resulting in expression of p21 at the time when the vector coding for the transgene of choice enters the cell.

7.

Use of overexpressed p21 to prevent apoptosis of target cells when a therapeutic gene is transferred

8.

A viral vector system to optimise the gene transfer which is characterized by a viral gene transfer vector that carries beside the transgene of choice or its cDNA a cDNA coding for p21.

9.

A viral vector system to optimise the gene transfer which is characterized by

- a viral vector which codes for the transgene of choice or its cDNA and
- a second viral transfer vector carrying a cDNA that codes for p21

10.

A viral vector system of claim 8 or 9 which is characterized by the fact that the viral vector system is an adenovirus-, retrovirus-, parvovirus-, herpes virus and/or baculovirus-vector.

Summary

The invented method for stabilization and improvement of gene transfer into mammalian cells is characterized by co-transfer and co-expression of a gene of choice or its cDNA and the gene of the cell cycle regulator $p21^{WAF1/CIP1}$ (p21) which prevents apoptosis of the target cell.

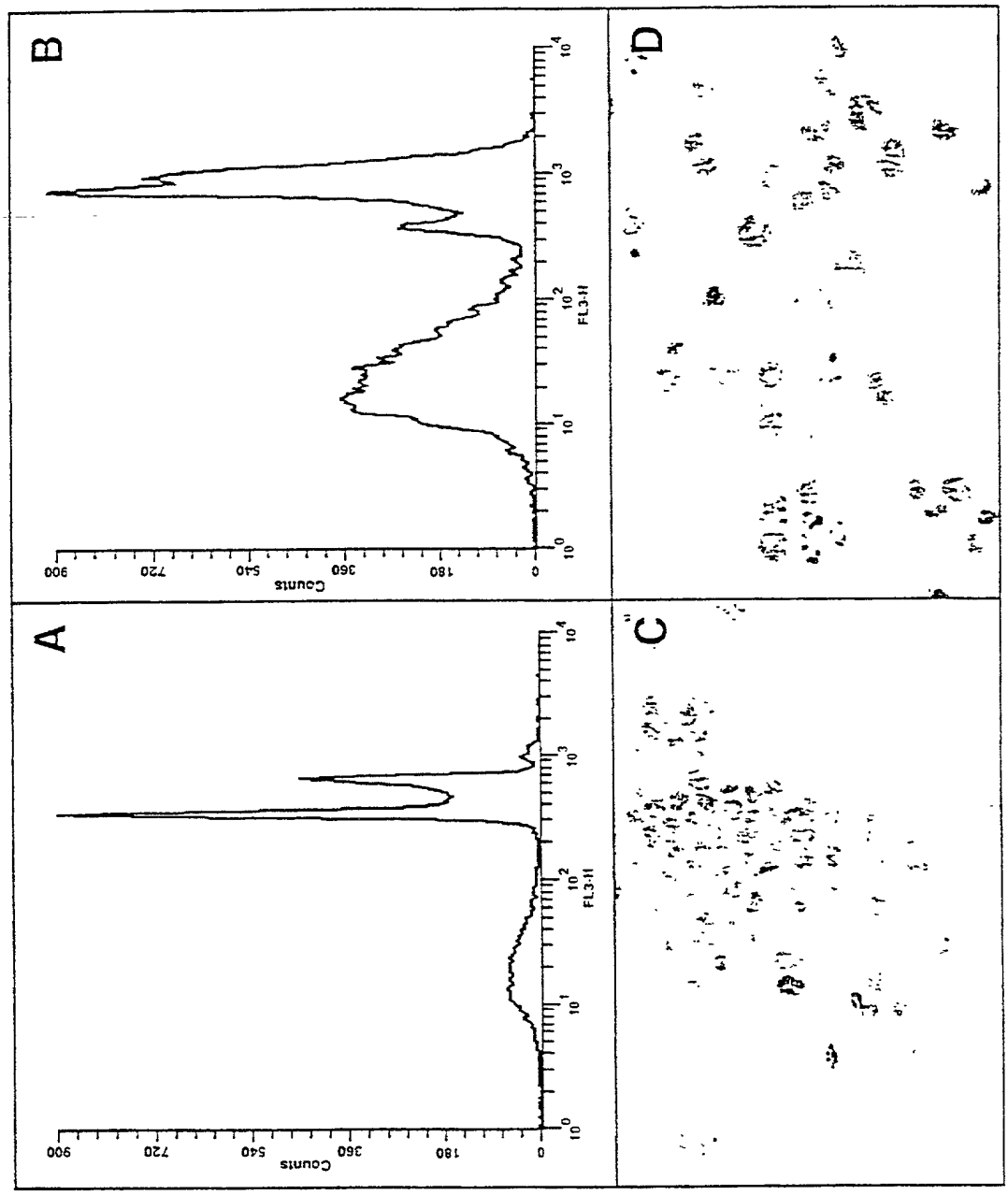

Fig. 1
Abbildung 1

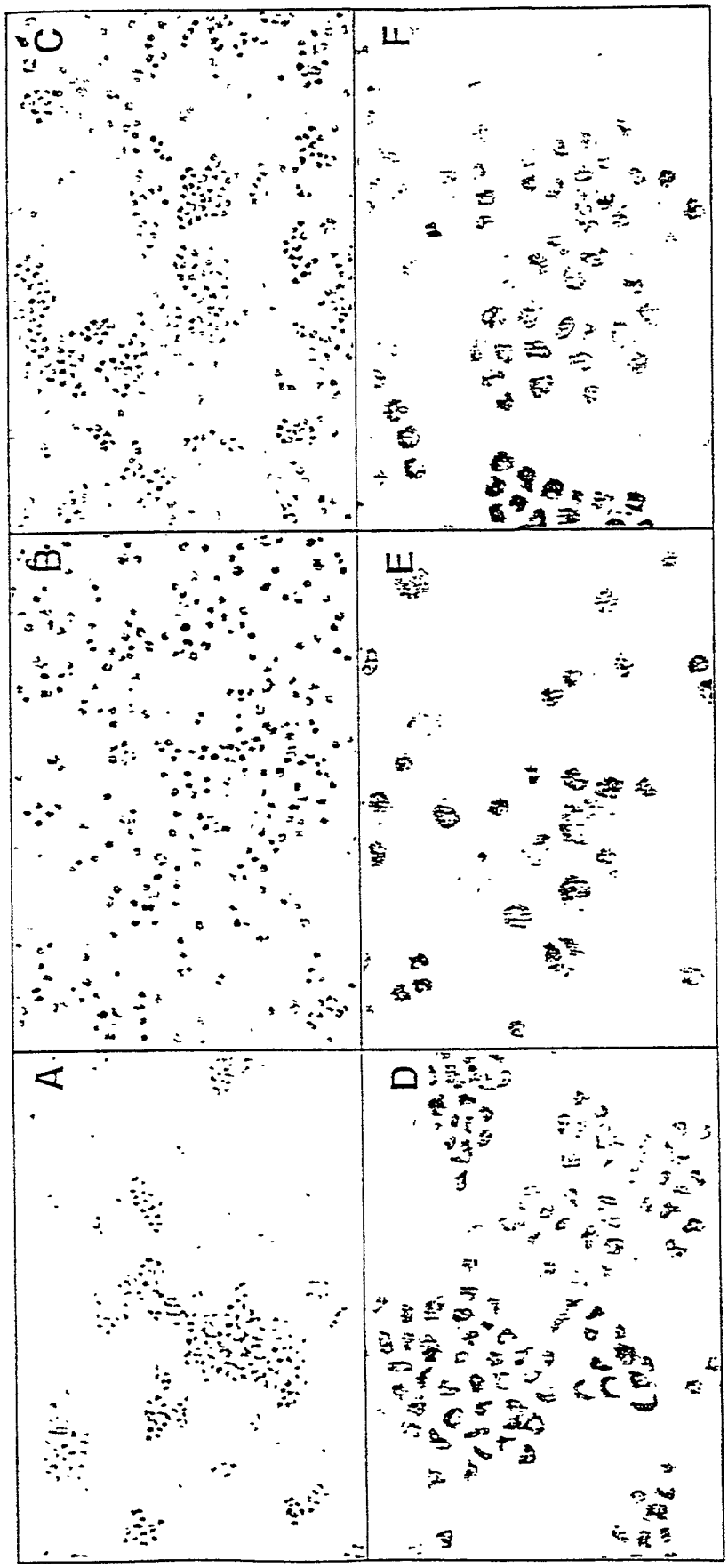

Fig. 2
Abbildung 2

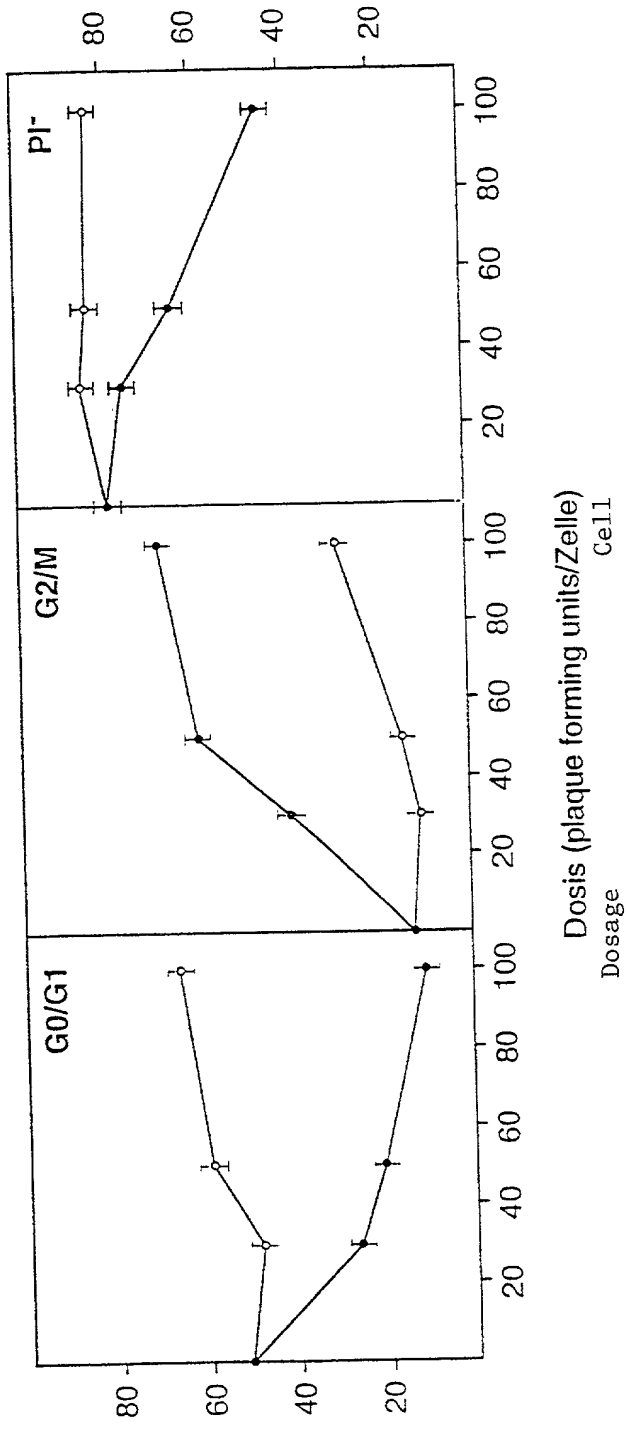

Fig. 3

Abbildung 3

Norris, McLaughlin & Marcus, P.A.

220 East 42nd Street, 30th Floor
New York, NY 10017

If each inventor understands English, the Declaration and Power of Attorney below is suitable for use when filing a regular patent application and also when entering the national stage, in the case of an International application designating the USA under the PCT.

COMBINED DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION	Attorney Docket No. 101195-38

As a below named inventor, I hereby declare that:
My residence, post office address and citizenship are as stated below next to my name,
I believe I am the original, first and sole inventor (if only one name is listed below at 201) or an original, first and joint inventor (if plural names are listed below at 201-205) of the subject matter which is claimed and for which a patent is sought on the invention entitled

Method for Improving the Gene Transfer of Genetic Material in Mammalian Cells Through the Use of P21 (WAF-1)

the specification of which (check one)

____ is attached hereto

_✓___ was filed on _____12 July 1999 ✓_____

under Serial Number _PCT/DE99/02180_✓ and was amended on _____
(if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, Section 1.56.

I list below any prior foreign application(s) for patent or inventor's certificate in respect of which foreign priority benefits are claimed under 35 USC 119; and any prior foreign application(s) for patent or inventor's certificate in respect of which such foreign priority rights are not claimed and which has a filing date before that of any application in respect of which such foreign priority benefits are claimed:

Application Number	Country	Filing Date (day, month, year)	Priority Claimed under 35 USC 119
198 30 874.4 ✓	**Germany** ✓	**10 July 1998** ✓	YES: ✓ NO:
			YES: NO:
			YES: NO:

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below.

Application No.	Filing Date

Combined Declaration and Power of Attorney
101195-38
Page 2

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

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10 –

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205	Family Name	First Given Name	Second Given Name
	City of Residence	State or Foreign Country	Country of Citizenship
	Post Office Address	City	State & ZIP/Country

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signature of Inventor 201 Bernd Dürkes	Date 01/11/01
Signature of Inventor 202	Date 01/08/01
Signature of Inventor 203	Date 01/08/01
Signature of Inventor 204	Date
Signature of Inventor 205	Date